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Genetic and environmental effects on body mass index from infancy to the onset of adulthood: an individual-based pooled analysis of 45 twin cohorts participating in the CODATwins study

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Running head: Heritability of BMI in childhood and adolescence

Abbreviations

-2LL= -2 log-likelihood

Δ =change

95% CI= 95 percent confidence interval

A=additive genetic variance component

a^2 =the proportion of total variance explained by additive genetic factors, heritability

BMI=body mass index

C=shared environmental variance component

c^2 =the proportion of total variance explained by shared environmental factors

d.f.=degrees of freedom

DZ=dizygotic twin

E=unique environmental variance component

e^2 =the proportion of total variance explained by unique environmental factors

logBMI= natural logarithm of body mass index

MZ=monozygotic twin

SD=standard deviation

Not a clinical trial

Abstract

Background: Both genetic and environmental factors are known to affect body mass index (BMI), but detailed understanding of how their effects differ during childhood and adolescence is lacking.

Objective: We analyzed the genetic and environmental contributions to BMI variation from infancy to early adulthood and how they differ by sex and geographic regions representing high (North-America and Australia), moderate (Europe) and low levels (East-Asia) of obesogenic environments.

Design: Data were available for 87,782 complete twin pairs from 0.5 to 19.5 years of age from 45 cohorts. Analyses were based on 383,092 BMI measures. BMI variation was decomposed into genetic and environmental components through genetic structural equation modeling.

Results: The variance of BMI increased from 5 years of age along with increasing mean BMI. The proportion of BMI variation explained by additive genetic factors was lowest between 4 and 8 years of age ($a^2=0.41-0.74$) and again between 11 and 13 years of age in boys ($a^2=0.65-0.72$) as well as 13 years of age in girls ($a^2=0.57$). This was because of a stronger influence of environmental factors shared by co-twins at these ages. After 15 years of age, the effect of shared environment was not observed. The sex-specific expression of genetic factors occurred already in infancy, but was prominent at 13 years and later ages. Genetic variance of BMI was highest in North-America and Australia and lowest in East-Asia, but the relative proportion of genetic variation to total variation was roughly similar across different regions.

24 Discussion: Environmental factors shared by co-twins affect BMI in childhood and during puberty, but
25 little evidence for their contribution was found in late adolescence. Our results suggest that genetic
26 factors play a major role in the variation of BMI in adolescence in populations of different ethnicities
27 and exposed to different environmental factors predisposing to obesity.

28

29 Key words: BMI, children, genetics, twins, international comparisons

30

Introduction

Childhood obesity is a major public health problem throughout the world. In the USA, more than 30% of children and adolescents were classified as overweight or obese in 2011-2012 (1), and childhood obesity is also a growing problem in many developing countries (2). Previous twin and family studies have shown that both genetic and environmental factors contribute to obesity. As early as in 1923, the tendency toward obesity was found to vary between families, suggesting a role of genetic factors (3), and a recent meta-analysis of 31 twin studies showed that for adults the heritability estimates of body mass index (BMI), i.e. total BMI variation explained by genetic variation, ranged from 47% to 80% (4). However, much less is known about the variation of the genetic architecture of BMI during childhood and adolescence. A meta-analysis of nine twin studies found that the environmental factors shared by co-twins contributed to BMI in infancy and early childhood, but were not evident after mid-childhood when genetic factors become more important (5). An individual-based analysis of four twin cohorts found shared environmental contributions to BMI from 3 to 8 years of age, which disappeared at 9 to 19 years of age (6). Somewhat different results were found in a Finnish longitudinal study, which found that shared environment affected BMI at 11-12 and 14 years of age but was no longer evident at 17 years of age (7). Thus, previous twin studies suggest that the effect of shared environmental factors influencing BMI disappears in late adolescence when genetic factors explain around 80% of the variation of BMI.

However, little is known about the universality of these results considering that the two previous multinational analyses were primarily based on Western populations, with the exception of one Korean twin cohort. A multinational study pooling eight cohorts of adolescent twins found that the heritability estimates of BMI were approximately similar in Western and East-Asian populations even when the

mean BMI and total variation of BMI were higher in Western populations (8). However, it is still unknown whether the genetic architecture is similar at earlier ages. Furthermore, because of a lack of data in the previous multinational analyses (5,6), it is still unclear how genetic influences on BMI differ between boys and girls over infancy and childhood.

To answer these questions on differences in the genetic architecture of BMI during childhood and adolescence, we conducted an individual-based analysis pooling twin cohorts from different countries. Our very large sample size allowed us to estimate the proportions of BMI variation explained by genetic and environmental factors using 1-year age groups in boys and girls separately. We aimed (i) to estimate how the genetic architecture of BMI changes from infancy to the onset of adulthood, (ii) to study age and sex-differences in the contributions of genetic and environmental factors, and (iii) to analyze whether these estimates are similar in different geographic-cultural regions representing different levels of obesogenic environment.

Subjects and methods

The data were derived from the CODATwins (Collaborative project of Development of Anthropometrical measures in Twins) database described elsewhere (9). Briefly, the CODATwins project was intended to collect height and weight measurements from all twin cohorts in the world. For the present analysis, we selected 45 twin cohorts from 21 countries having at least 50 measures of height and weight from 0.5 to 19.5 years of age. We divided these cohorts into three geographic-cultural regions: Europe, North-America and Australia, and East-Asia. The prevalence of obesity and overweight is lowest in East-Asia, thus representing a lesser obesogenic environment, and highest in North-America and Australia thus representing a more obesogenic environment (10). We had 20

cohorts from Europe, 15 cohorts from North-America and Australia and seven cohorts from East-Asia. Furthermore, we had one cohort from Africa and two from the Middle-East. However, during the course of the study, we found that in a large Chinese National Twin Cohort Study, the heritability estimates of BMI were substantially lower than in other East-Asian cohorts as also reported previously (11). Given of this heterogeneity, we did not include this cohort in the reported analyses but tested how it would change the results in East-Asia. The names of the cohorts included in the analyses are given in the footnotes of **Supplemental table 1**, and more information on these cohorts is available elsewhere (9). We eliminated impossible values and outliers in each age and sex group based on visual inspection allowing the BMI distribution to be positively skewed. We removed 1151 measurements as outliers representing 0.3% of the measurements. Further we selected only one observation per twin individual for each 1-year age group. After these exclusions, we had 383,092 BMI values from 180,390 twin individuals (46% females) including 87,782 complete twin pairs (36% MZ twins, 37% same-sex DZ and 27% opposite-sex DZ twins) in the reported analyses. The number of complete twin pairs by age, zygosity and region is presented in Supplemental table 1. The number of BMI measures varied from 6,174 at six years of age to 31,708 at one year of age. The largest number of measures was available from Europe (N=278,479), followed by North-America and Australia (N=66,204), and finally East-Asia (N=36,528). In the additional analyses including the Chinese National Twin Cohort Study, the number of BMI measures in East-Asia was 55,756.

The data were analyzed using classical genetic twin modeling based on linear structural equations (12). Genetic twin modeling is based on the fact that MZ twins share virtually the same DNA sequence whereas DZ twins share, on average, 50% of their genes identical-by-descent. DZ within-pair correlations of BMI were more than half of the MZ correlations suggesting the presence of environmental effects shared by co-twins (Supplemental table 1). Thus we decomposed the trait

variation into (i) an additive genetic component (A), which is the sum of the effects of all alleles affecting the trait, (ii) a common environmental component (C) including all environmental factors shared by co-twins and (iii) an unique environmental component (E) reflecting the effects of all environmental factors that make co-twins dissimilar including measurement error. The additive genetic correlation is 1 between MZ co-twins and 0.5 between DZ co-twins, whereas the correlation between the shared environmental factors is 1 and that between unique environmental factors 0 both in MZ and DZ co-twins. All genetic models were fitted with the OpenMx package, version 2.0.1, which is part of the R statistical platform (13). All parameter estimates and corresponding 95% confidence intervals (95% CI) were estimated by raw-data maximum likelihood method. Heritability is defined as the proportion of total variation accounted for by additive genetic variation.

BMI showed increasing right skewness from 1 to 18 years of age, and thus we used a log-transformation to normalize the BMI distribution at all ages when calculating the relative proportions of genetic and environmental variation. Further, we adjusted BMI for age and study cohort differences within each 1-year age and sex group by calculating regression residuals. We tested the technical assumptions of twin modeling by comparing the ACE model to the saturated model, which specifies an unconstrained model for trait means, variances and co-variances between co-twins. The fit of nested models was compared by calculating differences in -2 log-likelihood values (Δ -2LL), which follows the χ^2 -distribution with a difference in degrees of freedom (Δ d.f.) that corresponds to the difference in the number of free parameters estimated. As reported previously, DZ twins had slightly higher mean BMI as well as higher standard deviation (SD) compared to MZ twins at some ages over childhood and adolescence (14). We therefore allowed different means for MZ and DZ twins, but in the genetic models constrained variance components to be the same in all zygosity groups within sex.

126

127 The model fit results are presented in **Supplemental table 2**. At most of the ages, the fit of the full
128 ACE model was significantly poorer than the fit of the saturated model, because of the higher SD of
129 BMI in DZ twins. Even when the differences were small, they were statistically significant because of
130 our very large sample size. Moreover, we tested possible sex differences by constraining the A, C and
131 E parameter estimates to be equal in boys and girls. We found that at most ages, the fit of this model
132 was poor suggesting that these variance components differed between sexes. We also tested whether
133 this difference was because of different variances of logBMI in boys and girls by fitting a scaled model
134 allowing different sizes of variance components but fixing the relative size of these components to be
135 equal. This model also showed significant differences compared to the full ACE model. Accordingly,
136 we presented results separately for boys and girls. Finally, we tested whether a partly different set of
137 genes affects BMI in boys and girls by fitting a sex-limitation model. This model tests whether the
138 genetic correlation of opposite-sex DZ twins is lower than 0.5. We found evidence of a sex-specific
139 genetic effect at some ages seen also as lower opposite-sex DZ correlations (Supplemental table 1 and
140 2). Therefore, sex-specific genetic effects were allowed at all ages.

141

142 We then explored how age modified the genetic and environmental variance components by using
143 gene-environment interaction models (15), where variance components A, C and E were allowed to
144 vary as a function of age. In these models, BMI instead of logBMI was analyzed because we were
145 interested in analyzing how the variance of BMI varies as a contrast to standardized variances studied
146 by univariate models. Given that the parameter estimates differed in males and females (Δ -2LL=514,
147 Δ d.f.=15, p-value < 0.0001), we conducted models separately in boys and girls. Because the size of the
148 sex-specific genetic effect varied according to age, we used only same-sex pairs in these age-
149 moderation analyses. In addition to linear effects of age, we also included quadratic age effects on the

variance components because these were highly significant in males (Δ -2LL=844, Δ d.f.=3, p-value < 0.0001) and females (Δ -2LL=495, Δ d.f.=3, p-value < 0.0001). In all models, we adjusted mean BMI for the effects of age, age-squared, and study cohort.

The pooled analysis was approved by the ethical board of the Department of Public Health, University of Helsinki. The data collection procedures of participating twin cohorts were approved by local ethical boards following the regulations in each country. Only anonymized data were delivered to the data management center at University of Helsinki (9).

Results

Mean BMI decreased from infancy, reaching a nadir at 5 years of age in boys and girls before increasing until 19 years of age in the pooled data (**Table 1**). Along with the increasing mean BMI, the variance of BMI also started to increase after 5 years of age. The increase in mean BMI started in Europe after 5 years of age, but slightly later in East-Asia (6 years) and in North-America and Australia (7 years). Boys were slightly heavier than girls from 1 to 4 years of age and again from 17 to 19 years of age, but at other ages sex differences were small. In Europe and North-America and Australia, BMI variances were higher in girls than in boys, especially in adolescence and early adulthood. North-American and Australian boys and girls had the highest mean BMI at all ages, and this difference increased after 7 years of age. European boys and girls had also slightly higher BMI than East-Asians at most ages. Similar differences were also seen in the BMI variation, and at all ages variances were highest in North-America and Australia.

Figure 1 presents the relative proportions of logBMI variation explained by additive genetic, shared environmental and unique environmental factors in the pooled data. The proportion of shared environmental variation was largest between 4 and 8 years of age and subsequently heritability estimates were lower at these ages in boys and girls ($a^2=0.41-0.74$). The heritability estimates increased after 8 years of age, but in boys they were somewhat lower again between 11 and 13 years of age ($a^2=0.65-0.72$) when the contribution of shared environment was more important again. In girls a lower heritability estimate was seen at 13 years of age ($a^2=0.57$). After 15 years of age, the shared environmental variation was no longer present and thus heritability estimates were higher ($a^2=0.75-0.84$). The proportion of logBMI variation accounted for unique environmental factors was largely similar at all ages ($e^2=0.10-0.20$) and did not show any clear age pattern. The age pattern was similar in boys and girls in spite of the significant sex differences in the relative variance components at most ages (Supplemental table 2). Furthermore, genetic correlations within opposite-sex DZ pairs were generally lower than 0.5, suggesting sex-specific genetic effects, especially in adolescence (**Figure 2**).

We then fitted similar univariate models for logBMI by region. Only the estimates of additive genetic factors are presented in **Figure 3**, but all estimates with 95% CIs are available in **Supplemental table 3**. In Europe and North-America and Australia, the age-related differences in heritability estimates were largely similar to those in the pooled data. Additive genetic factors generally explained the lowest proportion of logBMI between 4 and 8 years of age in boys and girls, which was because of the higher impact of shared environmental factors at these ages. Moderate estimates of shared environmental variation were also seen between 12 and 14 years of age, but after that shared environmental variation diminished (Supplemental table 3). In East-Asia, the pattern was not as clear due to the smaller sample size and larger 95% CIs. However, as in the other regions, the heritability estimates increased in East-Asia after early childhood (6 years in boys and 4 years of girls) because of the diminishing effect of

shared environmental effects. In spite of the roughly similar age patterns, the proportions of logBMI variation explained by genetic and environmental factors were significantly different between the regions at all ages (Supplemental table 2). When the Chinese National Twin Cohort Study was included in the East-Asia region, the proportion of genetic factors decreased and shared environmental factors increased dramatically; the change was from 0.1 to 0.4 unit depending on the age group (data available on request).

Finally, we examined how age modifies the genetic and environmental variances of BMI. **Figure 4** presents the results by graphs, and all parameter estimates with 95% CIs are available in **Supplemental table 4**. In the pooled data, additive genetic variance increased steadily from 1 to 15 years of age in boys and to 19 years of age in girls. Shared environmental variances were largest from 10 to 15 years of age and disappeared after that. When comparing the regions, the general pattern was similar for Europe and North-America and Australia. However, both additive genetic and shared environmental variances were larger in North-America and Australia than in the other two regions, especially in girls. In East-Asia the shared environmental variance was still present at the onset of adulthood, especially in boys. The differences between the regions were highly significant in males (Δ -2LL=3490, Δ d.f.=30, p-value <0.0001) and females (Δ -2LL=3996, Δ d.f.=30, p-value <0.0001).

Discussion

In this very large study of nearly 400,000 BMI measures in nearly 88,000 complete twin pairs from 21 countries, we found that the age pattern of the genetic architecture of BMI from infancy to the onset of adulthood was more complex than previously suggested. As in two previous international studies (5,6),

we found that the proportion of BMI variance explained by shared environmental factors was most prominent from 4 to 8 years of age and it was not present in late adolescence between 15 to 19 years of age. However, shared environmental variation was also significant in early adolescence between 11 and 13 years of age. The onset of puberty and consequent large changes in body composition take place between these ages in boys and girls (16). Previous studies have provided evidence that shared environmental factors partly account for the timing of puberty in girls; for boys the results are less clear, but this may also be because the onset of puberty is more difficult to assess in boys than in girls (17,18). It is thus possible that shared environmental factors affect BMI through the timing of puberty at these ages (19).

The most systematic result of the present study is the increasing role of genetic factors in BMI across development, starting in infancy and continuing through late adolescence. Previous molecular genetic studies have indeed found that the variants of FTO gene, which account for the largest fraction of variance in BMI among the known candidate genes for BMI (20), and other obesity related candidate genes have increasing effects on BMI after 6 years of age (21-24). Evidence of increasing heritability of BMI from 4 to 10 years of age has also been reported in genome-wide complex trait analysis (25). These findings based on molecular genetic studies correspond with our results on the increasing genetic variation with age. However, this increasing role of genetic factors in BMI with age does not negate the importance of health behaviors associated with childhood obesity, as genetic factors can affect BMI by modifying food intake and other behavioral factors. For example, the variants of FTO gene, which act on the actual functional gene IRX3 (26), were found to be associated with food-intake self-regulation and eating styles in childhood which are further associated with weight gain (27). Although not yet conclusive, there is evidence that common genetic risk variants of BMI are active in the hypothalamus, pituitary gland, hippocampus and limbic system, i.e., areas of brain having an important role in appetite

regulation, learning, cognition, emotion and memory (28). It has also been found that shared environmental factors have effects on nutritional intake in childhood (29), but they disappear in adulthood when genetic factors become more important (30,31). The increasing genetic variation in BMI may thus reflect the increasing independence of children from their parents in eating and other behavioral factors associated with the variation of BMI. However, the associations between energy intake and obesity are complex and still an object of debate (32). Differences in DNA methylation have also been found between lean and obese children (33), and epigenetic processes by themselves are in part genetically regulated (34). Therefore, it is possible that part of the genetic variation may be mediated by epigenetic effects.

We found some evidence for sex-specific genetic contributions to BMI. The lowest genetic correlation within opposite-sex DZ pairs was found at 13 years of age probably coinciding with the onset of puberty. However, a sex-specific genetic contribution was also clear after puberty, which probably reflects the increasing differences in body composition between boys and girls with age (16). This is consistent with the sex-specific genetic contribution in adult BMI found in a study of twin cohorts with opposite-sex twins from 7 countries (35). However, it is noteworthy that lower genetic correlations for opposite-sex pairs were found even in infancy, indicating that a partly different set of genes regulates BMI prior to the major hormonal changes that occur during puberty. This suggests some caution when interpreting results from genetic studies that have relied upon BMI pooling of boys and girls, even while focusing on pre-pubertal children. Otherwise, there were relatively minor differences in the genetic architecture of BMI between boys and girls, and the general age patterns were largely similar.

When comparing regions, North-American and Australian children and adolescents presented greater means and larger total variation of BMI than their European and East-Asian peers. The relative

proportions of genetic and environmental sources of variations were, however, roughly similar in these three regions. These results are consistent with those of previous international twin studies showing larger mean and variance of BMI, yet similar heritability estimates in Caucasian and in East-Asian populations in adolescence (8). Thus, increasing BMI was associated with increasing variation in BMI, caused substantially by genetic variation. This suggests that genetic factors have an important role in individual differences in BMI in various populations differing in ethnicity, environmental exposures, as well as in their possible interactions. These results are consistent with studies in Denmark (36) and Sweden (37) suggesting that both total and genetic variation of BMI increased during the obesity epidemic. It is, however, noteworthy that we limited our East-Asian cohorts to affluent populations including the affluent Shandong and Guangdong provinces but excluding poorer areas of China. As reported previously, the heritability estimates of BMI were much lower and common environmental estimates higher in other areas of China (11), which may indicate larger differences between families in nutritional status. This emphasizes the importance of collecting data on twins living under different environmental exposures.

The data used in this study have both strengths and weaknesses. The main strength is the very large sample size allowing an investigation of the change of the genetic and environmental contributions to individual differences in BMI in much more detail than in previous studies. We also have twin participants from different countries, thereby making it possible to stratify the analyses by regions of various ethnicities and obesogenic environments. Individual-based data also have many advantages as compared to literature-based meta-analyses, such as better opportunities for statistical modeling and lack of publication bias. However, even when the large majority of the twin cohorts in the world participated in this project, our data still had only limited power for East Asia, especially in adolescence. Another important limitation is that there were only few data sets available from the

Middle East and Africa, and a lack of data from South-America. This underlines the need for new data collection in these geographic regions. There were some violations of the assumption of twin modeling due to the larger variation in DZ twins than in MZ twins at some ages (14). The differences in the variation are, however, small and become statistically significant because of the very large sample size of our data. Finally, we did not have any area-level indicators and classified the cultural-geographic areas as less or more obesogenic based on the prevalence of adult obesity (10). Conceptualizing obesogenic environments is difficult, but it has been suggested that both micro- and macro-level environmental factors affect both food intake and physical exercise (38). More detailed measurements of the physical environment are thus needed to analyze the factors in the environment that potentially modify genetic influences on the development of obesity.

In conclusion, we found evidence that environmental factors shared by co-twins contribute to BMI variation in early childhood and during puberty, but their role diminishes before the onset of adulthood. Genetic variation increased steadily during childhood and adolescence, which may indicate gene-environment correlation processes, whereby an increasing independence of children from their parents led them to express their behaviors according to their genetic background. Genes affecting BMI were partly sex-specific, even in infancy, with their contribution becoming more prominent during and after puberty. Obesogenic environment is associated with increasing genetic variation of BMI in North-America and Australia as compared to East-Asia, but the relative proportions of genetic and environmental variations were roughly similar. Our results suggest that, in spite of different ethnicities and environmental exposures, genetic factors play a major role behind the variation of BMI in adolescence in affluent societies.

Conflicts of interests

None

Authors' contribution

KaSi, JaKa, ThIASø, DoIBo, FiRa, KiOKy, YMHu and YoYo planned the study design of the CODATwins project. AnBu, ChKa, KiJSa, KeLJa, WeCo, AmEHw, ThMMA, WeGa, CaYu, LiLi, RoPCo, BrMHu, KaCh, AxSk, KiOKy, ThIASø, CaADe, RoFVl, RuJFLo, JaKa, KaHe, JaWa, ClHLL, AbFi, ToAMc, ThCEl, AlMGr, MiHe, XiDi, MoBjAn, HeBeNi, MoSo, AddTa, DaLTa, MaAS, CoFa, CrDI, SyOo, ArKnNo, DaMa, LiAb, SAlBu, KeLKL, HeHMa, LiJEa, JuLSi, RoFKr, MaMc, ShPa, MaGa, DaABu, DoIBo, GoWi, ToCEMBe, MeBa, ChHo, JeMCR, RiSa, DuLFr, JoAMa, FuJi, FeNi, ZePa, LiDu, MiBo, MaBr, GiDi, FrVi, NiGMA, SaEMe, GrWMo, YMHu, BiKi, YoCh, ChHo, HyJSh, JaHGo, SöMö, JaHj, SaAa, ReSu, GaESw, RuKr, PaKEMa, NaLPe, AnKDA, FiRa, PeTy, PaLi, ClMAHa, RoPl, KPaHa, ElMTD, SeYOn, FaAl, GoBa, DaNa, TiSp, MaMa, GeLa, LaABa, CaTu, GlDu, DeBu, YoYo collected the data used in this study. KaSi and AlJe were in charge of data management. KaSi conducted the analyses, wrote the first draft of the manuscript and has primary responsibility of for final content. All authors have commented the manuscript and read and approved the final version of the manuscript.

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Table 1. Number of twin individuals and means and standard deviations (SD) of BMI by age and region in boys and girls.

| | N | All mean | SD | N | Europe mean | SD | North-America and Australia | | | East-Asia | | |
|--------------|-------|-------------|------|-------|----------------|------|-----------------------------|------|------|-----------|------|------|
| | | | | | | | N | mean | SD | N | mean | SD |
| Boys | | | | | | | | | | | | |
| Age 1 | 15919 | 17.1 | 1.38 | 13029 | 17.1 | 1.36 | 559 | 17.6 | 1.74 | 2238 | 17.1 | 1.40 |
| Age 2 | 13032 | 16.5 | 1.39 | 10677 | 16.5 | 1.37 | 617 | 17.4 | 1.54 | 1653 | 16.2 | 1.26 |
| Age 3 | 17334 | 15.9 | 1.46 | 14198 | 15.9 | 1.47 | 1063 | 16.4 | 1.79 | 2020 | 15.7 | 1.12 |
| Age 4 | 10118 | 15.9 | 1.82 | 7593 | 15.9 | 1.79 | 1512 | 16.1 | 2.17 | 1004 | 15.5 | 1.28 |
| Age 5 | 8255 | 15.3 | 1.57 | 6256 | 15.2 | 1.46 | 1096 | 16.0 | 2.09 | 880 | 15.2 | 1.20 |
| Age 6 | 3322 | 15.5 | 1.87 | 1450 | 15.5 | 1.59 | 811 | 16.0 | 2.60 | 1004 | 15.1 | 1.36 |
| Age 7 | 13767 | 15.4 | 1.82 | 11467 | 15.4 | 1.78 | 716 | 16.0 | 2.71 | 1269 | 15.3 | 1.51 |
| Age 8 | 6502 | 15.8 | 1.96 | 4491 | 15.7 | 1.84 | 695 | 16.4 | 2.84 | 1273 | 15.6 | 1.69 |
| Age 9 | 7066 | 16.5 | 2.43 | 4339 | 16.4 | 2.22 | 1430 | 17.3 | 3.15 | 1263 | 16.0 | 1.94 |
| Age 10 | 11531 | 16.7 | 2.38 | 9151 | 16.6 | 2.27 | 863 | 17.9 | 3.32 | 1388 | 16.6 | 2.19 |
| Age 11 | 9149 | 17.4 | 2.70 | 6739 | 17.3 | 2.57 | 963 | 18.6 | 3.58 | 1444 | 17.2 | 2.36 |
| Age 12 | 12140 | 18.0 | 2.90 | 8673 | 17.6 | 2.66 | 2396 | 19.4 | 3.54 | 1071 | 17.8 | 2.55 |
| Age 13 | 5108 | 18.7 | 3.06 | 3629 | 18.3 | 2.63 | 1175 | 19.9 | 3.91 | 304 | 18.5 | 2.78 |
| Age 14 | 9687 | 19.5 | 3.07 | 6994 | 19.1 | 2.68 | 2525 | 20.6 | 3.76 | 168 | 18.9 | 2.73 |
| Age 15 | 5904 | 20.0 | 3.18 | 4341 | 19.5 | 2.62 | 1411 | 21.5 | 4.15 | 140 | 19.0 | 3.05 |
| Age 16 | 8745 | 20.8 | 3.02 | 6387 | 20.4 | 2.54 | 2213 | 21.9 | 3.86 | 128 | 19.9 | 3.33 |
| Age 17 | 11646 | 21.2 | 2.78 | 7681 | 21.0 | 2.61 | 3843 | 21.8 | 3.02 | 106 | 20.3 | 2.61 |
| Age 18 | 17407 | 21.7 | 2.66 | 7332 | 21.4 | 2.57 | 9925 | 21.9 | 2.71 | 123 | 20.3 | 2.34 |
| Age 19 | 11216 | 22.0 | 2.72 | 5605 | 21.7 | 2.47 | 5478 | 22.3 | 2.92 | 122 | 20.8 | 2.77 |
| Girls | | | | | | | | | | | | |
| Age 1 | 15789 | 16.7 | 1.37 | 12709 | 16.7 | 1.35 | 591 | 16.9 | 1.53 | 2381 | 16.7 | 1.39 |
| Age 2 | 12499 | 16.1 | 1.37 | 10081 | 16.1 | 1.35 | 590 | 16.8 | 1.49 | 1731 | 15.9 | 1.33 |
| Age 3 | 17602 | 15.6 | 1.51 | 14257 | 15.7 | 1.52 | 1107 | 16.0 | 1.89 | 2179 | 15.4 | 1.18 |
| Age 4 | 9842 | 15.7 | 1.90 | 7360 | 15.7 | 1.99 | 1442 | 15.8 | 2.21 | 1022 | 15.3 | 1.28 |
| Age 5 | 7984 | 15.1 | 1.65 | 6019 | 15.0 | 1.53 | 1026 | 15.8 | 2.33 | 918 | 15.1 | 1.30 |
| Age 6 | 2852 | 15.4 | 1.91 | 900 | 15.5 | 1.70 | 794 | 15.8 | 2.49 | 1092 | 15.0 | 1.38 |

| | | | | | | | | | | | | |
|--------|-------|------|------|-------|------|------|------|------|------|------|------|------|
| Age 7 | 13942 | 15.5 | 2.01 | 11528 | 15.5 | 2.03 | 735 | 15.6 | 2.61 | 1384 | 15.2 | 1.46 |
| Age 8 | 6160 | 15.8 | 2.15 | 4014 | 15.9 | 2.13 | 706 | 16.5 | 2.94 | 1417 | 15.4 | 1.60 |
| Age 9 | 6746 | 16.6 | 2.62 | 3903 | 16.6 | 2.49 | 1402 | 17.3 | 3.35 | 1404 | 15.8 | 1.82 |
| Age 10 | 11445 | 16.8 | 2.58 | 8975 | 16.8 | 2.52 | 840 | 18.0 | 3.50 | 1494 | 16.3 | 2.07 |
| Age 11 | 8962 | 17.6 | 2.95 | 6460 | 17.6 | 2.85 | 972 | 19.0 | 3.95 | 1527 | 16.8 | 2.17 |
| Age 12 | 12282 | 18.1 | 2.98 | 8572 | 17.8 | 2.74 | 2527 | 19.6 | 3.51 | 1183 | 17.5 | 2.32 |
| Age 13 | 4861 | 18.9 | 3.16 | 3299 | 18.7 | 2.87 | 1255 | 19.9 | 3.77 | 307 | 18.1 | 2.51 |
| Age 14 | 10221 | 19.8 | 3.16 | 7376 | 19.4 | 2.73 | 2677 | 21.0 | 3.87 | 168 | 18.5 | 2.43 |
| Age 15 | 5820 | 20.3 | 3.29 | 4217 | 19.8 | 2.78 | 1414 | 21.9 | 4.12 | 178 | 19.4 | 2.43 |
| Age 16 | 9611 | 20.7 | 3.07 | 7269 | 20.4 | 2.78 | 2180 | 21.8 | 3.73 | 155 | 19.9 | 2.25 |
| Age 17 | 10381 | 20.8 | 2.94 | 8632 | 20.6 | 2.68 | 1599 | 22.0 | 3.87 | 126 | 20.7 | 2.64 |
| Age 18 | 8775 | 21.2 | 3.16 | 6318 | 20.8 | 2.66 | 2291 | 22.4 | 4.03 | 133 | 19.9 | 2.35 |
| Age 19 | 9469 | 21.4 | 3.22 | 6558 | 21.0 | 2.75 | 2765 | 22.5 | 3.96 | 131 | 20.2 | 2.20 |

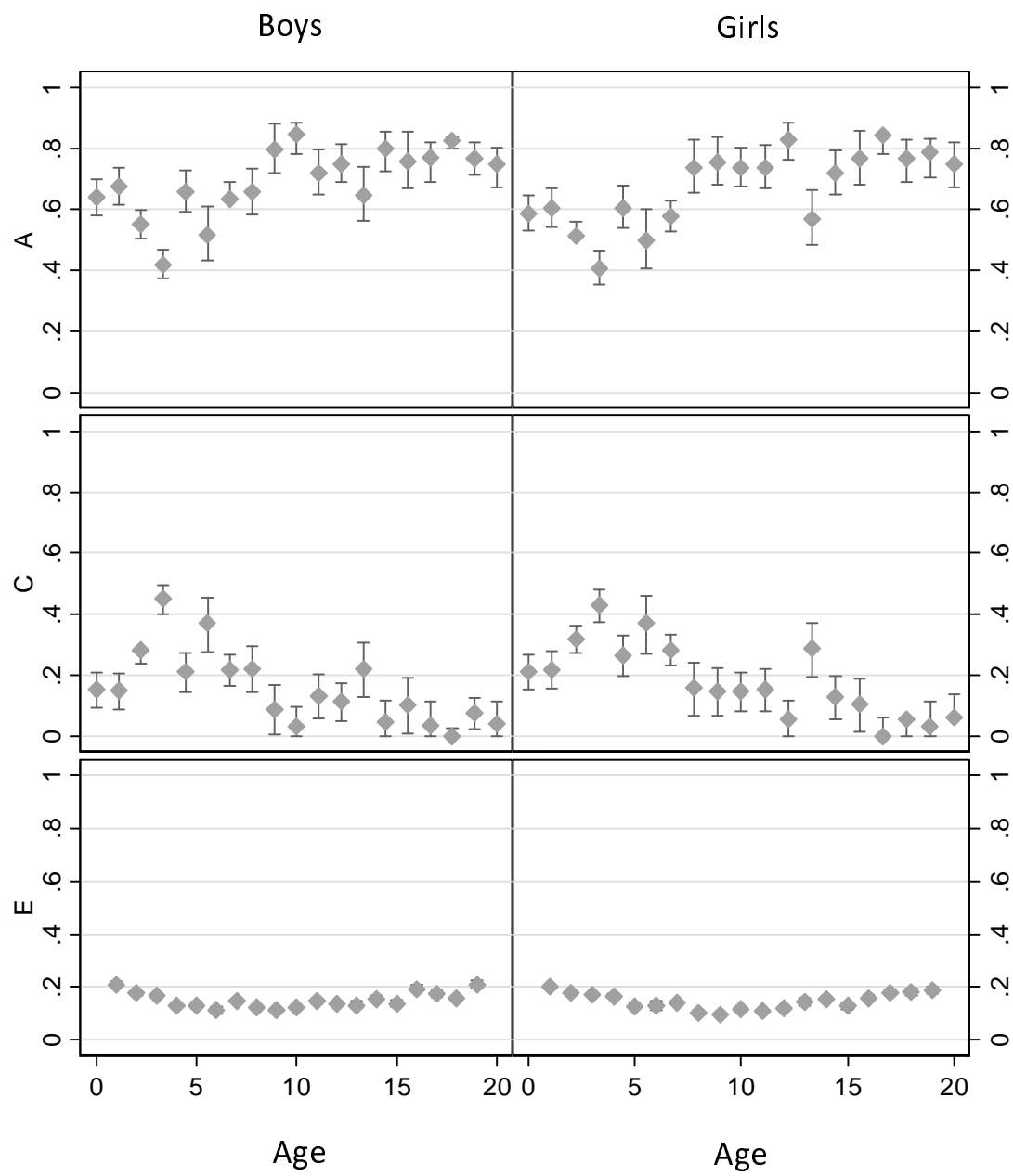
Figure legends

Figure 1. Proportions of logBMI variation with 95% confidence intervals explained by additive genetic, shared environmental and unique environmental factors by age and sex.

Figure 2. Additive genetic correlations with 95% confidence intervals within opposite-sex DZ pairs by age.

Figure 3. Proportions of logBMI variation with 95% confidence intervals explained by additive genetic factors by age, sex and region.

Figure 4. Changes of additive genetic (dash line), shared environmental (solid line) and unique environmental (dot line) variance with increasing age in quadratic gene–environment interaction model by sex and region.



correlation

